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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,040	06/21/2005	Thomas Schmehl	080618-0576	4643

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EXAMINER	
SHOMER, ISAAC	
ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,040	SCHMEHL ET AL.	
	Examiner	Art Unit	
	ISAAC SHOMER	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-25 and 27-52* is/are pending in the application.

4a) Of the above claim(s) *15, 16, 19, 20, and 27-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-14,17,18,21-25 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed after a final rejection on 19 April 2010, have been fully considered. In light of applicants' arguments, the finality of the previous action has been withdrawn, prosecution is hereby reopened, and this action is made non-final.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

For the purposes of examination under the prior art, the term "encapsulated," as of claim 11, will be broadly interpreted to read on both the encapsulation of a hydrophilic substance in a liposome by its storage in the inner aqueous space of said liposome, as well as encapsulation of a hydrophobic substance by entrapment in the bilayer of the liposome. This determination is made in light of the fact that prostacyclin, a known hydrophobic compound, is "encapsulated" into the liposomes in the instantly claimed method as of claim 51.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 11, 12, 14, 17, 18, 21, 22, 25, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mautone (US Patent 5,306,483).

Mautone is drawn to drug delivery of pharmaceuticals by aerosolizing said drug into mammalian lungs, as of Mautone, column 1 lines 9-11. In one embodiment, Mautone describes a vehicle system for pulmonary drug delivery comprising DPPC:CP[1]:PG[2] in a ratios of about 7:0.35:1, as of Mautone, column 4 lines 5-10. In a separate embodiment, Mautone teaches that, sphingomyelin, cholesteryl palmitate, and phosphatidylglycerol all act as spreading agents (Mautone, column 3 lines 10-20) wherein said spreading agents are useful in that they assist DPPC in rapidly forming a spread film on the air/liquid surfaces of the lungs, as well as maintaining balance and stability in the lungs, as of Mautone, column 2 lines 4-10. DPPC is suggested to be present in the concentration range of 80.0% to 99.5% by weight, and other agents such as spreading agents including sphingomyelin are suggested to be present in the range of 0.5% to 20.0% by weight, as of Mautone, column 5 lines 17-25. Administration in the form of liposomes is suggested as of Mautone, column 3 lines 24-26 and lines 43-47. Administration via nebulizer is suggested as of Mautone, column 10 lines 63-68. Multilamellar vesicles are suggested as of Mautone, column 2 lines 50-51.

The specific combination of features claimed is disclosed within the broad generic ranges taught by the reference but such "picking and choosing" within several variables does not necessarily give rise to anticipation. Corning Glass Works v. Sumitomo Elec., 868 F.2d 1251, 1262 (Fed. Circ. 1989). Where, as

[1] Cholesteryl palmitate, which is interpreted to read on "a cholesterol lipid" as of claim 11.

here, the reference does not provide any motivation to select this specific combination of variables specifically DPPC, cholesteryl palmitate, and sphingomyelin in the form of a liposome, anticipation cannot be found.

That being said, however, it must be remembered that "[w]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v. Teleflex, 127 S,Ct. 1727, 1740 (2007) (quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976)). "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is... a person of ordinary creativity, not an automaton." Id. at 1742.

Consistent with this reasoning, it would have obvious to have selected various combinations of various disclosed ingredients specifically DPPC, cholesteryl palmitate, and sphingomyelin in the form of a liposome from within a

[2] Phosphatidylglycerol

prior art disclosure, to arrive compositions "yielding no more than one would expect from such an arrangement".

Mautone suggests that sphingomyelin and/or cholesteryl palmitate is to be present in the range of 0.5% to 20.0% by weight, as of Mautone, column 5 lines 17-25. This does not read on the claimed range of claim 18, but does overlap with it. While the prior art does not disclose the exact claimed values, but does overlap: in such instances even a slight overlap in range establishes a *prima facie* case of obviousness. In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003).

Claims 11-14, 17, 18, 21, 22, 24, and 25, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mautone et al. (US Patent 5,306,483) as applied to claims 11, 12, 14, 17, 18, 21, 22, and 25, and 52 above, and further in view of Taylor et al. (Thorax, Vol. 47, 1992, pp. 257-259).

Mautone teaches a method of pulmonary administration of a drug comprising administering a liposome comprising DPPC, cholesteryl esters, and sphingomyelin. Mautone suggests the addition of "other compounds" generically to affect the release rate of the drug from DPPC, as of Mautone, column 2 lined 40-45.

Mautone does not teach the elected species of cholesterol, wherein said cholesterol is not an ester. Mautone does not teach an air jet nebulizer.

Taylor et al. (hereafter referred to as Taylor) teaches air jet neublizer to administer a DPPC/cholesterol liposome with a drug to humans, as of Taylor,

page 258 left column, third full paragraph. Inclusion of cholesterol in the liposome is taught to increase the stability of the liposome and to decrease the rate of drug release, as of Taylor, page 258 right column, fourth paragraph. A slower rate of release (i.e. a controlled delivery) allows for a decreased frequency of dosing, with a reduction in systemic side effects, as of Taylor, page 258 right column, fourth paragraph. Taylor teaches that liposomes can remain intact for prolonged periods, as of Taylor, page 257 left column, bottom paragraph. Multilamellar vesicles are suggested as of Taylor, page 257 right column, first full paragraph.

It would have been prima facie obvious for one of ordinary skill in the art to have included cholesterol in the liposomes of Mautone. The skilled artisan would have been motivated to have done so in order to have decreased the rate of release of the active agent from the liposome delivered to the lung, thereby predictably reducing dosing frequency and decreasing systemic side effects with a reasonable expectation of success. The application of a known technique (using cholesterol to decrease rate of release) to a known method (liposomal administration to the lungs, as of Mautone) ready for improvement (less side effects) to yield predictable results is prima facie obvious. See MPEP 2143, Exemplary Rationale D.

While neither Taylor nor Mautone teach the percentage of liposomes that remain intact upon administration to the lungs, it appears reasonable to believe that the liposomes of Mautone would have remained intact upon pulmonary administration. This is because the liposomes of Mautone and Taylor appear to

be similar to the instantly disclosed liposomes comprising sphingomyelin[3] and because the use of air-jet nebulizers, as of Taylor, appears to result in stability in the range of 50% to 80%.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mautone et al. (US Patent 5,306,483) by itself or in view of Taylor et al. (Thorax, Vol. 47, 1992, pp. 257-259) as applied to claims 11-14, 17, 18, 21, 22, 24, 25, and 52 above, and further in view of Mihalko et al. (US Patent 5,340,587).

Mautone teaches a method of pulmonary administration of a drug comprising administering a liposome comprising DPPC, an ester of cholesteryl esters, and sphingomyelin. The teachings of Taylor suggest the addition of non-esterified cholesterol.

Mautone does not teach administration via an ultrasonic nebulizer.

Mihalko et al. (hereafter referred to as Mihalko) teaches the use of an ultrasonic nebulizer to form liposomes in aerosol form, as of Mihalko, column 9 lines 50-60, wherein said liposome aerosol appears to be useful for drug delivery via inhalation, as of Mihalko, column 1 lines 18-21.

It would have been prima facie obvious for one of ordinary skill in the art to have used an ultrasonic nebulizer to have delivered the liposomal composition of Mautone, optionally in view of Taylor. The skilled artisan would have been motivated to have done so because an ultrasonic nebulizer would have predictably delivered a liposomal composition via inhalation to the lungs with a

[3] See instant specification, page 8, Table 2, Example 3.

reasonable expectation of success. The application of a known technique (administration via ultrasonic nebulizer) to a known method (liposomal delivery to the lung, of Mautone) ready for improvement to yield predictable results is prima facie obvious. See MPEP 2143, Exemplary Rationale D.

Claims 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mautone et al. (US Patent 5,306,483) by itself or in view of Taylor et al. (Thorax, Vol. 47, 1992, pp. 257-259) as applied to claims 11-14, 17, 18, 21, 22, 24, 25, and 52 above, and further in view of Max et al. (European Journal of Pediatrics, Vol. 158 Suppl 1, 1999, pp. S23-S26).

Mautone teaches a method of pulmonary administration of a drug comprising administering a liposome comprising DPPC, an ester of cholesteryl esters, and sphingomyelin. The teachings of Taylor suggest the addition of non-esterified cholesterol. Taylor further suggests the entrapment of hydrophobic drugs in liposome bilayers (as of Taylor, page 258 left column, first full paragraph), for the purposes of pulmonary delivery.

Neither Mautone nor Taylor teach a prostacyclin.

Max et al. (hereafter referred to as Max) teaches the administration of prostacyclin to treat pulmonary hypertension via various routes including aerosolized delivery (i.e. pulmonary delivery), as of Max, page S23, abstract.

It would have been prima facie obvious for one of ordinary skill in the art to have used prostacyclin as the drug to be delivered in the liposomal delivery method of Mautone in view of Taylor. The skilled artisan would have been

motivated to have done so because administration of prostacyclin to the lungs via inhalation is suggested as of Max. As such, the skilled artisan would have been motivated to have predictably used prostacyclin as the specific drug in the method of Mautone or Taylor with a reasonable expectation of success. Generally, it is *prima facie* obvious to select a known material for incorporation into a composition, based on its recognized suitability for its intended use. See MPEP 2144.07.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/I. S./
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612